American Journal of Medical Genetics 63:382–385 (1996)

Brief Clinical Report

Cardio-Facio-Cutaneous (CFC) Syndrome: Report of an Adult Without Mental Retardation

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We report on a 25-year-old woman with typical manifestations of the cardio-facio-cutaneous (CFC) syndrome, but without mental retardation. She had valvular and infundibular pulmonic stenosis, brittle and woolly hair with patchy alopecia, scant body hair, dry and hypohydrotic skin, and characteristic facial traits. To our knowledge, this is the first case of CFC syndrome without mental retardation but typical cutaneous findings.

KEY WORDS: cardio-facio-cutaneous syndrome, mental retardation

INTRODUCTION

The cardio-facio-cutaneous (CFC) syndrome is a recently recognized multiple congenital anomalies/mental retardation (MCA/MR) syndrome. Since the first report of eight cases by Reynolds et al. [1986], at least 20 additional cases of the CFC syndrome have been described [Neri et al., 1987; Verloes et al., 1988; Chrzanowska et al., 1989; Mucklow, 1989; Sorge et al., 1989; Gross-Tsur et al., 1990; Piérard et al., 1990; Fryer et al., 1991; Blanchet-Bardon et al., 1991; Matsuda et al., 1991; Bottani et al., 1991; Corsello et al., 1991; Turnpenny et al., 1992; Mathews et al., 1993; Borradori et al., 1993].

Typical findings include a characteristic craniofacial appearance, psychomotor and growth retardation, congenital heart defects, and typical skin abnormalities [Buyse, 1990]. Some of these phenotypic manifestations bear close resemblance to those observed in Noonan syndrome; others are characteristic of CFC only.

Received for publication May 3, 1995; revision received November 20, 1995.

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We report on an additional case of CFC syndrome in a woman with typical manifestations, including cutaneous lesions, and without mental retardation.

CLINICAL REPORT

The patient is the second born of three sibs of healthy and nonconsanguineous parents. Family history is unremarkable. Pregnancy was uncomplicated; delivery was at term with normal birthweight.

Somatic and psychomotor development were at the lower limits of normal until the age 2 years, when a valvular and infundibular pulmonic stenosis was discovered and corrected surgically. Subsequently there was a significant improvement of growth and mental development. On a picture at the age of 3 years, the baby showed brittle and woolly hair, low posterior hairline and narrow forehead (not visible in the picture), scant eyebrows and eyelashes, fullness of periorbital tissues, ectropion of lower palpebral fissures, malar hypoplasia, bulbous nose, hyperplasia of the helix and of the ear lobe (Fig. 1).

The patient also presented prognathism and dental malocclusion with supernumerary teeth that were extracted at the age of 6 years. At the age of 18 years, she had a surgical correction of the severe prognathism.

The patient attended school up to 19 years with good results. No specific learning disabilities were reported to us. Presently she works as a secretary.

When she came to our service at the age of 25 for an evaluation of her reproductive risk, the physical examination showed weight 52 kg (25th centile), height 160 cm (25th–50th centile), head circumference 57 cm (over the 97th centile); macrocephaly, dolichocephaly, and narrow forehead, "coarse" face, down-slanting palpebral fissures with scant eyebrows and absent eyelashes on the nasal side, edematous eyelids and ectropion of the lower eyelids, apparent hypertelorism, strabismus, nystagmus, and myopia; posteriorly angulated ears with hyperplastic helix and lobes; highly arched and vaulted palate, malocculsion of teeth and prognathism; webbed neck (Figs. 2, 3).

Fig. 1. Frontal view of the patient at the age of 3 years showing brittle and woolly hair, decreased eyebrows and eyelashes, fullness of periorbital tissues and ectropion of lower palpebral fissures, malar hypoplasia, bulbous nose, hyperplasia of the helix and lobes.

Fig. 2 and 3. Frontal and lateral views of the patient at the age of 25 years showing macrocephaly, dolichocephaly, and narrow forehead, "coarse" face, down-slanting palpebral fissures with decreased eyebrows and absent eyelashes on the nasal side, edematous eyelids and ectropion of the lower lids, apparent hypertelorism, posteriorly angulated ears with hyperplastic helix and lobes, prognathism, webbed neck.

Her dermatological status included dry skin with patchy follicular hyperkeratosis, especially on the dorsal aspect of limbs, almost total alopecia of the body, with scant pubic hair and absence of axillary hair. The scalp was diffusely hyperkeratotic with brittle, woolly and dry hair, and with areas of alopecia (Fig. 4). Nails were hypoplastic. No café-au-lait spots were present.

No neurological and behavioural problems were noted.

The patient was counseled as having CFC syndrome and was given a 50% risk for affected children. We also discussed the chance of mental retardation in the offspring without giving specific figures.

DISCUSSION

The patient we describe has clinical manifestations of the CFC syndrome, including a characteristic facial appearance (especially on her childhood picture), typical congenital heart defect, nystagmus, strabismus and myopia, and a very severe ectodermal involvement (skin, eyelashes, eyebrows, teeth, finger and toenails) (Table I). The unusual aspect of this case is the phenotypic progression into adult age with lack of mental deficit. CFC syndrome is an MCA/MR syndrome whose nosology is still under debate. CFC and Noonan syndromes have some overlapping traits. The ectoder-

Fig. 4. View of the patient's scalp at age 25 years showing brittle, woolly and dry hair, and areas of alopecia.

TABLE I. Clinical Findings in Present Case Compared to Previous CFC Syndrome Cases

Clinical data	Present case[a]	Previous cases[b]
MR/developmental disability	–	26/26
Growth retardation	+	19/24
Relative macrocephaly	+	18/21
Distinctive face ("coarse" face)	+	23/26
Narrow forehead/temporal narrowing	+	16/24
Hypoplastic supra-orbital ridges	+	16/24
Down slanting palpebral fissures	+	17/24
Epicanthic folds	+	13/24
Palpebral ptosis	+	14/24
Depressed nasal bridge	+	17/24
Highly arched palate	+	13/24
Posteriorly angulated ears with prominent helix	+	20/24
Webbed neck	+	14/26
Abnormal hair (brittle/sparse/friable)	+	26/26
Alopecia areata	+	2/24
Hyperkeratotic skin lesions (dry/hyperkeratosis/ichthyosis)	+	23/26
Absent/decreased eyebrows	+	17/26
Eye abnormality	+	18/26
Heart defect	+	20/25
Splenomegaly	–	6/24
Hemangiomas	–	7/24
Herniae	–	6/24
Nail dystrophy	+	5/24

[a] + = present; – = absent.
[b] Previous cases: Reynolds et al., 1986; Neri et al., 1987; Verloes et al., 1988; Chrzanowska et al., 1989; Mucklow, 1989; Sorge et al., 1989; Fryer et al., 1991; Matsuda et al., 1991; Corsello et al., 1991; Turnpenny et al., 1992; Mathews et al., 1993; Borradori et al., 1993.

mal manifestations are the hallmark of the CFC syndrome [Neri et al., 1991], with hypotrichosis or brittle hair (or both) in all cases, hyperkeratosis in many cases, and scant eyebrows in some cases. Alopecia, dysplastic teeth, and nails and capillary haemangiomata are present occasionally [Borradori et al., 1993].

Ectodermal manifestations are thought to occur in about ⅓ of patients with Noonan syndrome, consisting mainly of hyperplastic skin, lymphoedema, nevi, café-au-lait spots, dystrophic nails, and curly hair [Turnpenny et al., 1992]. Noonan and CFC syndromes have an identical spectrum of congenital heart abnormalities (pulmonary valve stenosis, atrial septal defect) [Turnpenny et al., 1992].

Nystagmus was noted in three of the patients of Reynolds et al. [1986] and in both of the patients of Verloes et al. [1988], but this abnormality has not been reported in the Noonan syndrome [Fryer et al., 1991].

Mental retardation is said to be invariably present in the CFC syndrome [Turnpenny et al., 1992; Neri et al., 1991], although the mental status may improve during development, at least in some patients [Reynolds et al., 1986; Fryer et al., 1991].

Another condition that one must consider in the differential diagnosis is the Costello syndrome [Zampino et al., 1993]. In these two syndromes, there is striking phenotypic overlap. All the manifestations of the CFC syndrome may be present in the Costello syndrome and only the marked facial traits and clinical course are peculiar to Costello syndrome patients. Similarly, a condition that has to be considered in the differential diagnosis is the Noonan-like syndrome, cherubism, and polyarticular pigmented villonodular synovitis [Gorlin et al., 1990], which can be differentiated on the basis of the presence of chronic synovitis.

In the last few years many similar syndromes have been identified. CFC and Noonan syndromes are a typical example. Their clinical similarity might be the result of allelic or locus heterogeneity, or perhaps of modifying influences of other genetic or nongenetic factors. Studies at the molecular level will help to solve this intractable question. For the time being, we support the hypothesis of others [Neri et al., 1991; Turnpenny et al., 1992] that the CFC and Noonan syndromes are two distinct entities.

Finally, we hope that these studies will also help us to define more accurately the reproductive risk of these patients, especially for the aspect of mental retardation.

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